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Genotypic Tropism Testing of Proviral DNA to Guide Maraviroc Initiation in Aviremic Subjects

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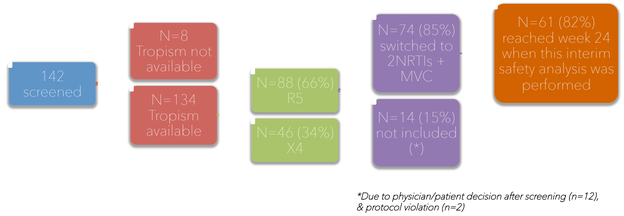
Background: Maraviroc (MVC) is a suitable drug for aviremic subjects on antiretroviral treatment (ART) developing toxicity, but its prescription requires prior tropism testing. It is unknown if proviral DNA genotypic tropism testing is reliable to guide MVC initiation in aviremic subjects.

Methodology: This was a Phase 4, prospective, single-arm study (ID: NCT01378910) in 24 HIV care centers in Spain. Participants were MVC-naive HIV-1-infected adults with HIV-1 RNA (VL) <50 c/mL on stable ART during the previous 6 months, requiring an ART change due to toxicity, with no antiretroviral resistance to the ART started and R5 HIV by proviral DNA genotypic tropism testing (defined as a Geno2Pheno FPR>10% in a singleton). Subjects fulfilling the inclusion criteria initiated MVC with 2 NRTIs, and were followed for 48 weeks. Virological failure was defined as 2 consecutive VL>50 c/mL. Here, we present a pre-specified interim virological safety analysis performed when at least 2/3 subjects reached week 24 of follow-up. Recent adherence was calculated as: (# pills taken/# pills prescribed during the previous week)*100.

Results: Out of 142 subjects screened, tropism results were available from 134 **(Figure 1)**. 46 (34%) were X4 and 88 (66%) R5. 74/88 (85%) subjects were included and switched to MVC +2 NRTIs, and 61/74 (82%) had reached week 24 when this analysis was performed. Of these, 20% were women, 31% MSM, 36% had CDC category C, 36% were HCV+ and 10% HBV+ **(Table 1)**. Previous ART included PIs in 33 (55%) subjects, NNRTIs in 26 (43%) and INIs in 1 (2%) **(Figure 2)**. Reasons for treatment change were dyslipidemia in 21 (34%) subjects, gastrointestinal symptoms in 11 (18%), psychiatric symptoms in 3 (5%) and "other" in 26 (43%). Median CD4+ counts were 616 cells/mm^3 at screening and median nadir CD4+ counts were 143 cells/mm^3. MVC was given alongside TDF/FTC in 32 (52%) subjects, ABC/3TC in 26 (43%), AZT/3TC in 2 (3%) and ABC/TDF in 1 (2%) **(Figure 2)**. The evolution of CD4+ counts, total cholesterol, glycemia and recent adherence through week 24 is shown in **Figure 3**. 51 (84%) subjects maintained VL<50 c/mL through week 24, whereas 10 (16%) discontinued treatment: 2 (3%) withdrew informed consent, 1 (2%) was lost to follow-up, 1 (2%) developed an ART-related adverse event (rash), 2 (3%) died due to non-study-related causes (1 myocardial infarction at week 0 and 1 lung cancer at week 36), and 4 (6%) developed virological failure **(Figure 4)**.

Conclusions: In this interim 24-week virological safety analysis, initiation of MVC plus 2 NRTIs in aviremic subjects based on genotypic tropism testing of proviral HIV-1 DNA was associated with low rates of virological failure up to week 24.

Figure 1: Subject disposition.



*Due to physician/patient decision after screening (n=12), & protocol violation (n=2)

Table 1: Subjects' characteristics at baseline

Characteristic	
Female Gender, n (%)	12 (20%)
Age, median (IQR), n (%)	49 (43, 55)
Transmission route, n (%)	
MSM	19 (31%)
HTS	17 (28%)
IDU	19 (31%)
Other /Unknown	6 (10%)
CDC Category C, n (%)	22 (36%)
HCV coinfection, n (%)	22 (36%)
HBV coinfection, n (%)	6 (10%)
CD4+ counts (cells/mm^3), median (IQR)	
At screening	616 (472, 760)
Nadir	146 (60, 266)
HIV-1 RNA (copies/mL), median (IQR)	<50 (<50, <50)
Total cholesterol (mmol/L), median (IQR)	5.0 (4.3, 5.6)
Glycemia (mmol/L), median (IQR)	5.2 (4.9, 5.9)
AST (U/L), median (IQR)	37 (25, 62)

Figure 2: (A) Reasons for ART switch, (B) Previous ART and (C) NRTI backbone prescribed alongside MRV

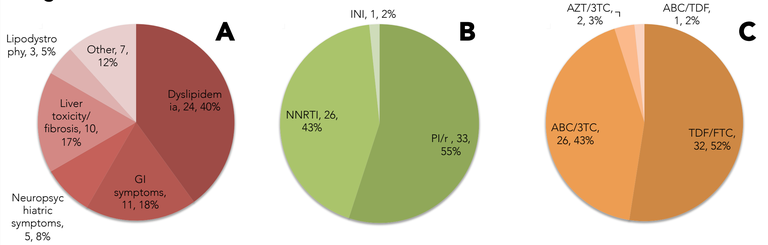


Figure 3. Evolution of CD4+ counts, total cholesterol, glycemia and recent adherence through week 24 (median and IQR values)

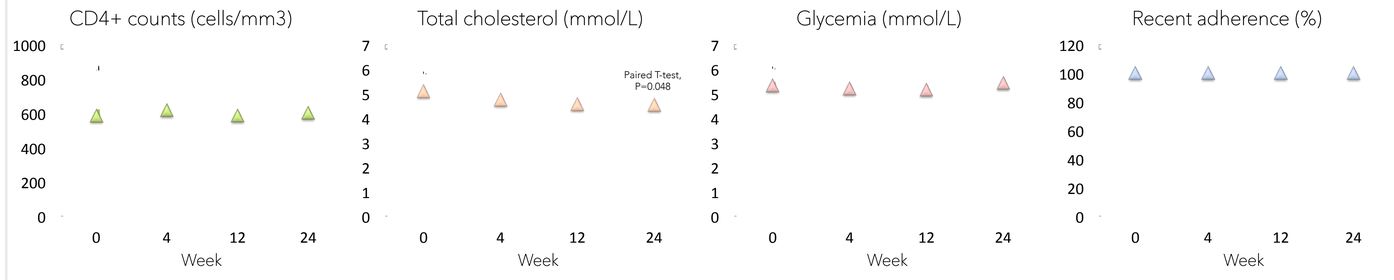
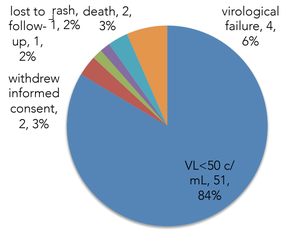


Figure 4. Study outcomes (Interim 24-week pre-specified safety analysis)



Characteristics of subjects developing virological failure

Subject	ART	Week of VF	HIV-1 VL at VF (c/mL)	Tropism at VF (FPR, %)	Recent adherence at VF	Resistance mutations at VF (IAS-USA 2013)	Salvage ART	Regained VL <50 c/mL with salvage ART
1	MVC+TDF/FTC	4	300	X4 (0.1)	100%	NA	DRV/r+ETV	Yes
2	MVC+TDF/FTC	12	14,102	X4 (1.3)	100%	RT: 41L, 67N, 184V, 215Y PR: 36I, 63P	TDF/FTC+ETV	Yes
3	MVC+ABC/3TC	24	416	R5 (52.1)	100%	RT: 90I, 184I PR: 64V	TDF+DRV/r+EFV	Yes
4	MVC+TDF/FTC	12	59	NA	100%	NA	MVC+TDF/FTC	Yes

** ART: Antiretroviral therapy; VF: virological failure; VL: HIV-1 RNA levels; RT: reverse transcriptase; PR: Protease; NA: not available; Recent adherence was calculated as: (# pills taken during the previous week/ # pills prescribed during the previous week)*100*

Conclusions:

In this interim 24-week virological safety analysis, initiation of MVC plus 2 NRTIs in aviremic subjects based on genotypic tropism testing of proviral HIV-1 DNA was associated with low rates of virological failure up to week 24. CD4+ counts and glycemia remained stable, but median total cholesterol improved through week 24. Adherence was 100% in the 3 upper quartiles.

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